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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/986,240	10/19/2001	Johan Weigelt	13425-047001	5027

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EXAMINER

DAVIS, DEBORAH A

ART UNIT	PAPER NUMBER
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1641

DATE MAILED: 11/06/2003

15

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application N .

09/986,240

Applicant(s)

WEIGELT ET AL.

Examiner

Deborah A Davis

Art Unit

1641

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 September 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-12 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-12 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

REQUEST FOR RECONSIDERATION

1. Applicant's argument filed September 24, 2003, in Paper #14 is acknowledged. Applicant argues that prior art did not teach the limitation that the potential binder molecule has a molecular mass of from 50-1000 Da. Arguments was carefully considered and found persuasive.

Withdraw Finality

2. Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn.

3. Applicant's arguments, see page 6, lines 1-14, filed September 24, 2003, with respect to the rejection(s) of claim(s) 1, 4-5, 8-10 and 12 under 35 U.S.C. 102(b) and claims 2-3 and 6-7 under 35 U.S.C. 103(a) have been fully considered and are persuasive. Therefore, these rejections have been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of Graham J. Moore, 35 U.S.C. 103(a).

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

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invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. Claims 1, 4-5, 8-10, and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yabuki et al (Journal of Biomolecular NMR, 11: 1998) in view of Graham J. Moore (USP#6,060,603).

Yabuki et al teaches a method for stable-isotope labeling of proteins by cell free synthesis. In this method, a technique that utilizes Ras protein samples in which the main chain carbonyl carbons of one amino acid type (AA1) are labeled with ^{13}C carbons and another amino acid type (AA2) is labeled with ^{15}N are evaluated with HNCO-type NMR and 2D1-H-15N NMR (see NMR measurements, pg 299 and pg. 300, Figure 1). The amino acid Ser³⁹ (AA2) occurs directly subsequent to Asp³⁸ (AA1) as recited in claim 1 (pg. 301, paragraph 1). Yabuki et al evaluates several amino acid labeled pairs by NMR techniques; such as, the amino acids Asp and Ser are labeled in a pair located within the Ras protein (pg. 300, paragraphs 1 and 2). The labeled Ras protein was then complexed with the binder protein Raf RBD, and evaluated with NMR HNCO spectrum and then compared with the results of the NMR spectrum of labeled amino acid pairs (pg. 301, paragraph 1 and pg 302, Figure 3). Chemical shift differences such as cross peaks of labeled amino acid pairs of the Ras protein were observed, compared, recorded both by itself and complexed with the Raf RBD, indicating interaction between the labeled Ras protein and the Ras complexed with the binding protein as recited in claim 1 (pg. 300, last paragraph and pg. 301, first paragraph). The Ras-Raf RBD complex has a molecular mass of about 30 kDa as recited in claim 8 (pg. 300, last paragraph). The reference points out that labeled amino acid pair, Pro-Thr is unique in

the Ras protein and was identified by the HNCO experiments as recited in claims 4 and 5 (pg. 300, paragraph 5, lines 17-19). This dual labeling technique can be performed on very large proteins with a molecular mass of about 150 kDa (pg. 296, paragraph 2). Thus, dual labeling and site-directed labeling by cell-free protein synthesis will be useful techniques for analyzing the structures of proteins as recited in claim 12 (pg. 305, last paragraph, last 3 lines).

Yabuki et al does not teach that the potential binder molecule has a molecular mass from 50-1000 Da.

However, Graham J. Moore teaches the use of NMR techniques which are employed to evaluate tertiary structures of biological active ligands that has a molecular weight of < 500 or > 2000 Daltons (col. 3, lines 1-46) and also includes through-bond coupling patterns within a molecule (col. 13, lines 22-50). Preferably, when analyzing by NMR, the ligand should have a molecular weight of less than 3,000 Daltons.

It would have been obvious to one of ordinary skill in the art to modify the teachings of Yabuki et al to include the use of small molecular weight ligands to evaluate tertiary structures of biological active ligands as taught by Graham J. Moore. Further, absent evidence to the contrary, the range recited in the instant claims from 50-1000 Daltons is viewed as mere optimization of the prior art assay.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. Claims 2-3 and 6-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yabuki et al in view of Graham J. Moore and in further view of Fesik et al (WO97/18471)

The teachings of Yubuki et al and Graham J. Moore are set forth above and differ from the instant claims by not teaching the sphere radius of the labeled amino acid pair, the proximity of an active site within the protein, neither does Yabuki mention the result of the above described method is compared to the result of any other binding or activity assay.

However, Fesik et al teaches a method for identifying ligands which bind to a specific target molecule labeled with radioactive isotopes and said ligand binding is evaluated by NMR. Studies were also performed to compare binding constants of ligands to various biomolecules, determined by the NMR method, such as enzymatic, filter binding and gel shift screening assays (pg. 26, lines 18-24 and pg. 27, lines 1-9). An advantage of using NMR in screening assays is the ability to correlate observed chemical shifts from two-dimensional NMR correlation spectra with other spectra projections of target molecule configuration (pg. 24, lines 1-14).

It would have been obvious to one of ordinary skill in the art to incorporate a comparison method of the various assays as taught by Fesik et al into the method of Yabuki et al in view of Graham J. Moore to compare the binding of ligands to various biomolecules determined by NMR and to also observe chemical shifts from observed by

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2-D NMR techniques. With respect to claims 2, 3 and 6, one skilled in the art would recognized that the proximity and spatial orientations of amino acids within a protein can be modified in such a way to get the desired results, especially since it has been held that discovering an optimum value of a result effective variable involves only routine skill in the art. *In re Boesch*, 617 F.2d 272, 205 USPQ 215 (CCPA 1980).

Response to Arguments

8. Applicant's argument that Yabuki et al does not disclose the use of a potential binder molecule having a molecular mass from 50 to 1000 Da was found persuasive; however, a new ground of rejection is set forth above.

9. Applicant's argument that the WO 97/18471 reference does not add to what is lacking in Yabuki and provides no suggestion or motivation to modify Yabuki et al is not found persuasive because the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In the instant case, the WO 97/18471 reference teach the advantages of comparing NMR in screening assays to that of other spectra, which is the limitation lacking in Yabuki et al, and would therefore suggest to those of

ordinary skill in the art that the Yabuki et al in view of the WO 97/18471 can be combined to teach the instant invention.

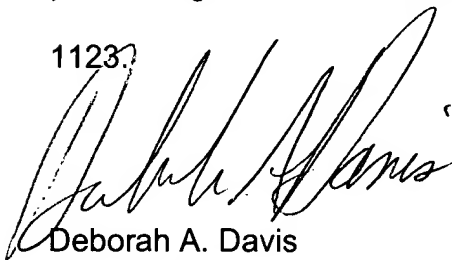
Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah A Davis whose telephone number is (703) 308-4427. The examiner can normally be reached on 8-5 Monday thru Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (703) 305-3399. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-

1123.



Deborah A. Davis
CM1, 7D16
October 15, 2003



LONG V. LE
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CP/03/03